DOCKET NO.: PMB9658 (ISIS-4502)

PATENT

REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 C.F.R. § 1.129

#80

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Plunkett
4/17/03

In re Application of: Tullis | **Confirmation No.: 9155**

Serial No.: 08/078,768 | **Group Art Unit: 1631**

Filing Date: June 16, 1993 | **Examiner: J. Martinell**

For: Oligonucleotide Therapeutic Agent And Methods Of Making Same

EXPRESS MAIL LABEL NO: EV 160093356 US
DATE OF DEPOSIT: March 7, 2003

Box AF
Assistant Commissioner for Patents
Washington DC 20231

Sir:

REPLY AND REQUEST FOR RECONSIDERATION PURSUANT TO 37 CFR § 1.129

This is in response to the Final Official Action dated September 10, 2002, issued in connection with the above-identified application. A petition for a three-month extension of time and Notice of Appeal are submitted herewith. Also submitted herewith is the fee under 37 C.F.R. §1.17(r) required for submission of a first response pursuant to 37 C.F.R. § 1.129. Reconsideration is respectfully requested in view of the following remarks and submissions.

REMARKS

Claims 64-83 are pending in the application. The invention defined by the pending claims is the product of the surprising discovery made by the Applicant more than twenty years ago that oligonucleotides may be used both *in vitro* and *in vivo* to regulate protein

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synthesis via hybridization to nucleic acids. Applicant's discovery enables the systematic design of oligonucleotide agents that block the translation of a target nucleic acid. The present invention was the product of keen scientific insight and extraordinary appreciation of a therapeutic regime which has proven to be highly useful and robust. The inventor made a breakthrough in the technology ... and did it in the face of skepticism on the part of others. Dr. Tullis's invention, which is reflected in an approved pharmaceutical as well as in a growing number of NDA applications before the U.S. Food and Drug Administration, exhibits all of the earmarks of brilliance – and patentability. The fact that the inventor made the invention very early in the field of oligonucleotide therapeutics is testimony to his work. Notwithstanding the fact that the science was still evolving and that the panoply of analytical and synthetic tools now available to the art was then only being developed, every test – every requirement for patentability of the present claims has been met.

In seeking patent protection for his discovery, Applicant presents independent claims 64, 73, 75, 78, and 80. Claim 64 encompasses methods for selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding both the target protein and other proteins without inhibiting the expression of the other proteins. This is done by synthesizing an oligonucleotide having a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid encoding the target protein. The oligonucleotide is introduced into the cell where hybridization of the oligonucleotide to the subsequence of the messenger ribonucleic acid occurs to inhibit the expression of the target protein.

Claim 73 recites methods for selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins

without inhibiting the expression of the other proteins. To accomplish this, one selects a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes and has a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of the cell encoding the target protein. The synthetic oligonucleotide is introduced into the cell and caused to hybridize with the messenger ribonucleic acid to inhibit the expression of the target protein.

The invention, as defined by claim 75, includes within its scope methods for selective inhibition of the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein without inhibiting the expression of the other proteins. One selects a synthetic oligonucleotide having enhanced resistance against nuclease enzymes and a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of the cell encoding the target protein. The synthetic oligonucleotide is introduced into the cell at a temperature between 0°C and 80°C to hybridize the synthetic oligonucleotide to the subsequence of messenger ribonucleic acid.

Claim 78 is directed to methods of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acid encoding the target protein by selecting a base sequence substantially complementary to the messenger ribonucleic acid of the cell encoding the target protein, providing a synthetic oligonucleotide that is stabilized against *in vivo* degradative enzymes and having the selected base sequence, and introducing the synthetic oligonucleotide into the cell to hybridize to the subsequence of the messenger ribonucleic acid.

As defined by claim 80, applicant's invention includes methods for selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids

encoding the target protein by selecting a plurality of base sequences that are complementary to the messenger ribonucleic acid, providing a synthetic oligonucleotide corresponding to each of the base sequences, selecting a preferred synthetic oligonucleotide for inhibition of the target protein in a cell, and using the selected oligonucleotide to inhibit the target protein in cells. Applicant's discovery has enabled the development of a vast array of therapeutic agents, including antibiotics and other drug substances that may address many unmet medical needs.

I. Applicant Seeks Withdrawal of the Finality of the Office Action under 37 C.F.R. § 1.129

The present rejection has been designated final. Applicant traverses.

As provided by 37 C.F.R. § 1.129, an applicant for a patent having an application pending for at least two years as of June 8, 1995, taking into account any reference made in such application to any earlier filed application under 35 U.S.C. § 120, 121, and 365 (c), is entitled to have a first submission entered and considered on the merits after final rejection where the first submission and the fee set forth in 37 C.F.R. § 1.17 (r) are filed prior to the filing of an appeal brief and prior to abandonment of the application, thereby automatically removing the finality of the rejection. The present application was filed June 16, 1993 but was pending for more than two years as of June 8, 1995 taking into account its parent applications including U.S. Application Serial Nos. 07/633,452, filed December 20, 1990, and 07/355,140, filed May 15, 1989. Applicant's earliest effective filing date is October 23, 1981, the filing date of parent U.S. Application Serial No. 06/314,124. Applicant has not submitted an appeal brief on the basis of the present final rejection, nor has Applicant abandoned the application. Accordingly, Applicant is entitled to the benefit of transitional

after-final practice under 37 C.F.R. §1.129, such practice allowing Applicant to submit, for example, an information disclosure statement, an amendment to the written description, claims, or drawings, a new substantive argument, and/or new evidence. *See* MPEP §706.07 (g).

Applicant requests withdrawal of the finality of the rejection and consideration of the evidence and arguments submitted herewith.

II. Claims 73-83 are Supported by the Specification

Claims 73-83 are rejected for alleged lack of written descriptive support under 35 U.S.C. §112, first paragraph. This is a new matter rejection, as the Examiner asserts there is no basis in the application for the various phrases to which objections have been raised. This is incorrect.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, diagrams, and formulas that fully set forth the claimed invention. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1656, 1572 (Fed. Cir. 1997). Possession may be demonstrated in a variety of ways including description of an actual reduction to practice, a showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formula that show that the invention was complete, or a description of distinguishing identifying characteristics sufficient to show that the applicant

was in possession of the claimed invention. *See Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68 (1998). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *See In re Wertheim*, 541 F.2d 257, 263 (C.C.P.A. 1976). Notably, while newly added claims or claim limitations must be supported in the specification through express, implicit, or inherent disclosure, there is no *in haec verba* requirement. *See* MPEP § 2163.

Claims 73, 75, and 78 are rejected for alleged lack of written description in the recitation of the phrase "substantially complementary." That phrase, however, is supported by the specification as filed, for example, in claims 20, 31, and 45; in the abstract ("a stabilized oligonucleotide ... having a base sequence substantially complementary to a portion of messenger ribonucleic acid coding for a biological component"); at page 4, line 28 to page 5, line 2 ("forming an oligonucleotide having a base sequence substantially complementary to a portion of mRNA coding for the specific biological component"); and at page 5, lines 18-21 ("synthesizing an oligonucleotide, the order of which is derived from the base sequence and substantially complementary to the messenger ribonucleic acid coding for the protein"). Again, the law does **not** require precisely identical wording, only **support** in the specification. Such is clearly present here.

Claims 73 and 75 also are rejected for alleged lack of written description in the recitation of the phrase "selecting a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes." That phrase is supported by the specification as originally filed, for example, at page 3, lines 11-16 ("a stabilized oligonucleotide ... is provided"); page 3, lines 26-28 ("synthesizing an oligonucleotide the sequence of which is derived from the base sequence"); page 17, lines 21-24 ("the oligonucleotide can then be modified to a nuclease

resistant phosphotriester form"); and page 18, lines 7-10 ("It is believed that transforming the oligonucleotide to a phosphotriester form will improve the oligonucleotide's stability *in vivo* due to an enhanced resistance against various degradative enzymes").

Claim 80 is rejected for alleged lack of written description in the recitation of the phrase "selecting a plurality of base sequences that are complementary to said messenger ribonucleic acid." That phrase is supported by the specification as originally filed, for example, at page 4, line 27 to page 5, line 2 ("forming an oligonucleotide having a base sequence substantially complementary to a portion of mRNA coding for the specific biological component"); page 9, lines 5-8 ("a synthetic oligonucleotide having a base sequence capable of substantially matching that of a chosen mRNA is provided"); page 10, lines 16-19 ("Once the sequence of the appropriate nucleic acid and the desired mRNA sequence have been determined, an oligonucleotide, complementary to the mRNA can be constructed."); and Example 2, particularly at page 19, lines 4-26 (demonstrating selection of the sequence to be hybridized with FSH mRNA).

Claim 78 is rejected for alleged lack of written support in the recitation of the phrase "providing a synthetic oligonucleotide that is stabilized against *in vivo* degradative enzymes." The language at issue in claim 78 is supported, however, in the application as filed, for example, at page 3, lines 11-16 ("a stabilized oligonucleotide … is provided") and at page 18, lines 7-10 ("It is believed that transforming the oligonucleotide to a phosphotriester form will improve the oligonucleotide's stability *in vivo* due to an enhanced resistance against various degradative enzymes").

Additionally rejected for alleged lack of written descriptive support is claim 81 in reciting the phrase "oligonucleotides stabilized against *in vivo* degradative enzymes." That

phrase is supported in the application as originally filed, for example, at page18, lines 7-10 ("It is believed that transforming the oligonucleotide to a phosphotriester form will improve the oligonucleotide's stability *in vivo* due to an enhanced resistance against various degradative enzymes").

Claim 75 is further rejected for alleged inadequate written descriptive support in recitation of the phrase "introducing said synthetic oligonucleotide into the cell at a temperature between 0°C and 80°C to hybridize said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid." Claim 75 is fully supported in the specification as originally filed, for example, at page 14, lines 1-4 ("while any theoretically suitable temperature may be used for the hybrid formation, temperatures ranging from 0°C to about 80°C provide for good hybridization").

One having ordinary skill in the art would reasonably conclude that Applicant was in possession of the invention as defined by claims 73-83 at the time of filing. Applicant requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

III. Claims 75 and 76 are Enabled

Claims 75 and 76 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The rejection must be withdrawn.

The enablement requirement of 35 U.S.C. § 112, first paragraph, mandates that the specification teach those skilled in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270 (1916)). The test of enablement is **not**

whether **any** experimentation is necessary, but whether, if experimentation is necessary, it is **undue**. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404.

The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of nonenablement must be based on the evidence as a whole. *See id.* In order to make a rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *See In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The burden then shifts to the applicant to provide persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973). The record is now replete with

evidence – facts – underscoring the enablement of the present claims. The Examiner has met these facts only with surmise and skepticism.

It is asserted that the method of *in vivo* nucleic acid molecular hybridization "at temperatures that kill cells" is not enabled. *See* Office Action at 3. Applicant disagrees. The temperature range for hybridization as set forth in claims 75 and 76 disclosed in the specification is not limited to *in vitro* applications. Organisms that survive at extreme temperatures were known in the art at the time of filing of the application. For example, *Thermus aquaticus* (Taq) thrives at an optimal temperature of 74°C, but remains functional and active up to about 95°C. Taq remains active at higher temperatures, but starts to lose activity over time at temperatures above 95°C. *See* Chien et al., *J. Bacteriology*, 127(3):1550-1557 (1976) (Exhibit A). As enablement does not require 100% success (*see Wands*, 8 U.S.P.Q.2d at 1406), the temperatures at the extremes of the range set forth in claims 75 and 76 are enabled even though not every cell type would survive at those temperatures.

Applicant requests withdrawal of the rejection.

IV. Claims 64-83 are Enabled

Claims 64-83 are rejected for alleged lack of enablement under 35 U.S.C. § 112, first paragraph. Applicant disagrees.

Preliminarily, Applicant notes that it has been asserted repeatedly that the present invention would not work *in vivo* using double-stranded oligonucleotides. Applicant has not limited his invention to single-stranded oligonucleotides, and the Examiner has cited no support for his allegation that a double-stranded oligonucleotide would not work in the

claimed methods as required for a rejection for alleged lack of enablement. Rather, Applicant asserts that double-stranded oligonucleotides work in the claimed methods. This assertion is supported, for example, by Crooke (*Annu. Rev. Pharmacol. Toxicol.*, 32:329-376 (1992) (Crooke 1992)) (Hecht Declaration Exhibit 4) at page 330.

A. Enablement Does Not Require that Applicant Expressly Teach Every Form of Stabilized Oligonucleotides Available at the Time of Filing in Order to Enable Stabilized Oligonucleotides

Section 112 requires the specification to be enabling only to persons "skilled in the art to which it pertains, or with which it is most nearly connected." *DeGeorge v. Bernier*, 226 U.S.P.Q. 758 (Fed. Cir. 1985). Thus, a patent need not teach, and preferably omits, what is known in the art. *See In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, 231 U.S.P.Q. 649 (Fed. Cir. 1986) ("A patent applicant need not include in the specification that which is already known to and available to the public."); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). It has long been the law that a person skilled in the art is deemed to possess not only basic knowledge of the particular art, but also "the knowledge of where to search out information" for section 112 purposes. *In re Howarth*, 210 U.S.P.Q. 689 (C.C.P.A. 1981).

Nowhere in the specification are the methods of the invention limited to phosphotriester-stabilized oligonucleotides. In fact, throughout the entirety of the specification, it is clearly stated that phosphotriester oligonucleotides are simply a representative example of the stabilized oligonucleotides that may be used in the methods of the invention. For example, the specification states at page 3, "[i]n a presently preferred embodiment of the invention, by way of example and not necessarily by way of limitation, a

stabilized oligonucleotide, preferably in a phosphotriester form, is provided . . . " and at page 4, "[t]he preferred oligonucleotide . . . for increased stability, may be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation during use." The application again states at page 5 that the oligonucleotide "can be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation. . . ." Given the language of the specification including "such as," "preferred," and variations thereof, one of ordinary skill in the art readily understands that other forms of stabilized oligonucleotides were contemplated and equally useful in the methods of the invention.

That other forms of stabilized oligonucleotides were known in the art at the time of filing has been established by the Declaration of Dr. Stanley T. Crooke and others. It is a fact that stabilized oligonucleotides suitable for use in the invention were known and were available to those of ordinary skill in the art in 1981. There is no countervailing evidence of record.

References of record in this application support this fact. For example, U.S. Patent No. 3,687,808 to Merigan et al. describes stabilized phosphorothioate oligonucleotides available as early as 1972. Miller et al. (*Biochemistry*, 13(24): 4887-4906 (1974) ("Miller 1974")) describe the stabilized alkylphosphotriester DNA analogs described in the application. Matzura and Eckstein (*Eur. J. Biochem.*, 3: 448-452 (1968)) describe the nuclease resistance of phosphorothioate oligonucleotides. Agarwal and Riftina (*Nuc. Acids Res.*, 6:9, 3009-3024 (1979)) show the synthesis of oligonucleotides containing methyl and phenylphosphonate linkages. DeClercq et al. (*Virology*, 42:421-428 (1970)) set forth the resistance of thiophosphate-substituted oligonucleotides to degradative enzymes. Befort et al. (*Chem.-Biol. Interactions*, 9:181-185 (1974)) report that ribonucleic acids stabilized by

methylation are taken up by cells and exhibit anti-viral activity. Miller et al. (*Biochem.*, 20(7): 1874-1880 (1981)) report a stabilized alkyl phosphonate DNA analog having activity *in vitro*.

Since the Examiner seems unconvinced, however, further materials have been submitted. Holy ("Synthesis and Biological Activity of Some Analogues of Nucleic Acids Components," in PHOSPHORUS CHEMISTRY DIRECTED TOWARDS BIOLOGY, W.J. Stec, Ed., Pergamon Press, 53-64, 1980) describes modified nucleotide analogs having hydroxyl-containing aliphatic chains that are stable *in vivo* and display inhibitory and substrate activities. Harvey et al. (*Biochem.*, 12(2):208-214 (1973)) describe 5'-terminal alkyl phosphorothioate groups as protecting groups in oligonucleotide synthesis. Malkievicz et al. (*Czech. Chem. Commun.*, 38:2953-2961 (1973)) demonstrate the use of alkyl thioyl moieties as blocking groups in oligonucleotide synthesis. That modified oligonucleotides other than phosphotriesters were known to one of ordinary skill in the art prior to Applicant's effective filing date is further evidenced by the review of Summerton et al. (*J. Theor. Biol.,* 78:77-99 (1979)).

Not only would one having ordinary skill in the art have readily understood that stabilized forms of oligonucleotides in addition to phosphotriesters were contemplated by the invention, but an artisan of ordinary skill also would have known of a number of available stabilized oligonucleotide forms as of the filing date. As Applicant is not required to teach what is known in the art, his burden has been met.

The enablement requirement does not require that the Applicant have presented experiments with each of the available forms of stabilized oligonucleotides to demonstrate that they actually work in the invention. Rather, enablement requires only that Applicant

have taught how to determine which stabilized oligonucleotides work in the invention without undue experimentation. Applicant has satisfied this burden by providing representative examples demonstrating his invention. One having ordinary skill in the art need only substitute for the phosphotriester oligonucleotides of Applicant's examples other known forms of stabilized oligonucleotides to determine their efficacy in the invention. This would not require undue experimentation on the part of an artisan of ordinary skill.

B. History has Proven the Naysayers of *In Vivo* Antisense Technology to be Incorrect; The Present Invention Was Complete and Fully Enabling in 1981

The Examiner has placed much reliance on the Gura (*Science*, 270: 575-577 (1995)), Rojanasakul (*Adv. Drug Delivery Revs.*, 18: 115-131 (1996)), and Hijiya (*PNAS USA*, 91:4499-4503 (1994)) articles allegedly to show that the present invention is not enabled for *in vivo* use. Applicant asserts that it is improper to base a conclusion of nonenablement upon these few references in view of the numerous other references cited throughout the prosecution of the present application, including those cited herein, which contradict their allegations. In support of this contention, Applicant submits herewith a Declaration of Dr. Sidney M. Hecht pursuant to 37 C.F.R. § 1.132.

Dr. Hecht is the J.W. Mallet Professor of Chemistry and Professor of Biology at the University of Virginia. He serves as Chairman of the Scientific Advisory Board of Orchid BioSciences, as a member of the Scientific Advisory Boards of Xenogen, Galileo Laboratories and Palumed, and as a consultant for Isis Pharmaceuticals. He is President of Pinnacle Pharmaceuticals and a member of the Board of Directors. Dr. Hecht also is a member of the Board of Directors of Orchid BioSciences. He serves as an Associate Editor

of the *Journal of the American Chemical Society* and sits on the Editorial Advisory Boards of *Anti-Cancer Drug Design*, *Bioconjugate Chemistry* and *Current Medicinal Chemistry-Anticancer Agents.*

From 1981 to 1987, Dr. Hecht held concurrent appointments at Smith Kline & French Laboratories, first as Vice President Preclinical R&D, then as Vice President Chemical R&D. He has been named an Alfred P. Sloan Fellow and a John Simon Guggenheim Fellow at the Max Planck Institut für Experimentelle Medizin at Göttingen. In 1991 Dr. Hecht served as a Professor Associé at the Muséum National d'Histoire Naturelle in Paris and Gastprofessor at the Eidgenössische Technische Hochschule in Zürich; he studied at the Museum again for six months during 2000. Dr. Hecht also has held numerous lectureships at other universities. He received the 1996 Cope Scholar Award of the American Chemical Society and was selected as Virginia's Outstanding Scientist for 1996. More recently he was presented with the 1998 Research Achievement Award of the American Society of Pharmacognosy.

As early as 1969, Dr. Hecht studied mechanisms of protein synthesis via gene expression and regulation thereof. As early as 1972, he co-authored scientific journal articles regarding these studies. Further he has studied the chemistry and biochemistry of nucleic acids since 1966. His decades of experience as a biological chemist have instilled in him a knowledge of mechanisms of expression of specific genes. In short, Dr. Hecht is a premiere authority in the field of gene expression.

Dr. Hecht first notes that any concerns raised by Gura, Rojanasakul, and Hijiya are directed to the clinical safety of *in vivo* use of antisense technology rather than at the efficacy of *in vivo* antisense methodologies. For example, Rojanasakul at page 118 queries "Can antisense work in living systems?" and responds by stating that while "there are studies

which indicate the ***relative safety*** of antisense [oligonucleotides] *in vivo* . . . ***non-specific side effects*** of [antisense oligonucleotides] have also been reported in mice." Rojanasakul goes on to say that these safety concerns "do not diminish the potential use of [antisense oligonucleotides] *in vivo*, and there are few examples of successful *in vivo* treatment in the absence of specialized delivery systems." *Id.* Rojanasakul continues, stating that "[c]onsidering the various obstacles that the antisense [oligonucleotides] must encounter prior to their action . . . ***the desired activity of [antisense oligonucleotides] is observed.***" *Id.* (emphasis added).

Likewise, Dr. Hecht notes that Gura, a non-research-performing reporter, avers that "some experts in the field . . . argue that clinical trials have begun far too soon." Gura at 575. Dr. Hecht explains that such concerns regarding the clinical safety of antisense oligonucleotides were elicited by the side effects detected in some animal studies. For example, Gura describes one set of experiments in which lethality in monkeys administered a one-time, high-dose injection occurred as well as another set of experiments in which a transient decrease in two kinds of white blood cells and changes in heart rate and blood pressure resulted from the high dose administered. *See id.* at 576.

Similarly, the assertion that Hijiya characterizes the field of antisense as being "in its scientific infancy" is misplaced, according to Dr. Hecht. Hijiya makes clear that antisense oligonucleotides worked therein: "The experiments reported herein serve as a paradigm of [oligodeoxynucleotide]-based therapeutics for human malignancies." Hijiya at 4503. Hijiya reasons that, although *MYB* is an effective gene target of antisense oligonucleotides in human melanoma, "further development of the antisense strategy will be needed before the successful application of this technique ***in the clinic*** can be anticipated." *Id.*

A demonstration of F.D.A. acceptable clinical safety is not required by the first paragraph of 35 U.S.C. § 112. Enablement does not require that the claimed invention satisfy the higher safety standards applied to drugs to be used in clinical trials. According to MPEP § 2107.03, "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.... [I]t is improper for office personnel to request evidence...regarding the degree of effectiveness [in humans] (underlining in original)." Enablement requires only that the application teach how to make and use the invention without undue experimentation. This requirement has been met: one having ordinary skill in the art would be able to make and use the invention without undue experimentation using only the application as a guide.

Moreover, no drug is free of toxic effects. *See* Fingl and Dixon (Chapter One, "General Principles", In THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 4th edition, L.S. Goodman and A. Gilman, Eds. (1970)) (Hecht Declaration Exhibit 2). This fact has been known for many years, as substantiated by Dr. Hecht, and is as true today as it was when first presented in this textbook. For some authors, to question the clinical safety of a new drug paradigm is not surprising. If raising such questions were to bar patentability of new drugs, there would be no new drugs. Accordingly, some toxic effects of antisense therapeutics are to be expected. Some expected toxic effects, however, are not an indication that antisense therapeutics do not work *in vivo*.

Indeed, Dr. Hecht attests that any concerns voiced by Gura, Rojanasakul, and Hijiya regarding the use of antisense technology *in vivo* have been proven to be wrong. The successes achieved in the field of antisense technology have been witnessed, thereby ratifying the views of proponents of antisense at the time of the invention and silencing, indeed

converting, many critics to what is clearly the correct view: antisense works *in vivo* as taught by the present application.

A number of articles that corroborate the *in vivo* success of antisense technology have been cited during prosecution of the present application. In addition thereto, Applicant submits herewith Mirabelli et al. (*Anti-Cancer Drug Design*, 6:647-661 (1991)) (Hecht Declaration Exhibit 3) which notes that antisense oligonucleotides have demonstrated activities against a broad array of targets, that "the therapeutic indexes of phosphorothioate oligonucleotides appear to be quite high," and that "certain phosphorothioates . . . are extremely well tolerated in animals." Mirabelli at 651. Mirabelli also provides evidence of successful *in vivo* trials of antisense oligonucleotides. *See, e.g.,* Mirabelli at 653.

Crooke 1992 corroborates the *in vivo* stability of antisense oligonucleotides, noting that nuclease activity of sera derived from different species varies, with human being the least active. *See, e.g.,* Crooke 1992 at 337. Additionally, modified oligonucleotides enter cells at pharmacologically relevant concentrations. *See id.* at 338-339. *In vivo* pharmacokinetic studies reveal that antisense oligonucleotides are rapidly and broadly distributed following administration in mice, rabbits, and rats. *See id.* at 342-343. Toxicity studies reveal that phosphorothioate oligonucleotides, for example, have high therapeutic indices and exhibit toxicity only at concentrations far in excess of concentrations at which therapeutic activity is observed. *See id.* at 344; 346-347.

Further confirmation of the enablement of Applicant's invention is found in Cossum (*J. Pharm. and Exp. Ther.*, 267(3):1181-1190 (1993)) (Hecht Declaration Exhibit 5). That reference describes several *in vivo* studies in which phosphorothioate oligonucleotides were shown to be widely distributed following *in vivo* administration in nothing more than

phosphate buffer at physiologic pH. *See, e.g.,* Cossum at 1181-1182, 1186. Additionally, Cossum acknowledges that the dosages at which non-antisense effects occur are significantly greater than those at which antisense effects are observed. *See id.* at 1181.

Stepkowski et al. (*J. Immunol.*, 153:5336-5346 (1994)) (Hecht Declaration Exhibit 6) demonstrates specific inhibition of intercellular adhesion molecule-1 (ICAM-1) expression by antisense molecule IP-3082, thereby promoting heart allograft survival. *See* Stepkowski et al. at 5338. Extension of *in vitro* studies to *in vivo* analyses confirmed the correlation between the efficacy of antisense technology in a Petri dish and in a living organism.

Additionally, numerous patents have issued with claims directed to the *in vivo* use of antisense oligonucleotides. *See, e.g.,* U.S. Patent No. 6,498,147 ("Suppression of nuclear factor $_{K}$B dependent processes using oligonucleotides." See particularly claims 7-19.); U.S. Patent No. 6,489,307 ("Antisense compositions targeted to β1-adrenoceptor-specific mRNA and methods of use." See particularly claims 52-59 and 63-65.); U.S. Patent No. 6,479,465 ("Methods of treating colitis using STAT-4 antisense oligonucleotides." See particularly claims 1-7, 9, and 10.); and U.S. Patent No. 6,475,998 ("Methods and compositions for the treatment of injury to the central nervous system." See particularly claims 1-10, 18, and 19.).

Indeed, a search of the art of "antisense" in the PubMed database reveals approximately 16,986 references that demonstrate the extensive interest of the scientific community in the technology of the presently claimed invention (Hecht Declaration Exhibit 7). While surveying the teachings of each of the 16,986 references is not practicable, Applicant submits that not only has the Examiner failed to consider references which run contrary to the few references upon which he relies to assert a lack of enablement, but the Examiner is relying upon statements that have been proven false.

It requires no citation of authority to observe that the Courts have long and uniformly held that the making of an invention in the face of skepticism by the scientific community is a hallmark of nonobviousness. Were the Examiner's views on the topic of enablement to prevail, the same skepticism which provides a powerful indication of nonobviousness would simultaneously eviscerate patentability under the enablement standard. This cannot be the law.

It is asserted in the Office Action that the time lapse between the effective filing date of the present application and the numerous references cited in support of enablement of claims 64-83 weighs heavily against the claim that the instant application provides sufficient guidance to one of skill in the art to practice the claimed invention as early as the effective filing date of the instant application. As Dr. Hecht attests in the declaration submitted herewith, had the pharmaceutical industry in 1981 immediately applied its existing knowledge of medicinal chemistry and pharmacology to the teachings of Applicant, it would have practiced the present invention. Various factors contributed to the lag, not the least of which included establishment, within an organization, of an internal "champion" for a new technology paradigm where the champion is willing to sponsor and defend reallocation of resources from existing programs to a new program. Additionally, once acceptance of the new paradigm is made, established pharmaceutical practice requires pharmacologists to perform substantial and numerous pre-clinical studies to determine the toxicological profile, pharmacokinetics, and pharmacodynamics of any potential drug. Thus, according to Dr. Hecht, it is not unexpected that the generation and reporting of pre-clinical and clinical studies by the pharmaceutical industry related to the efficacy of a potential drug does not immediately follow the publication of the first few positive *in vitro* results.

It has been observed by Fingl and Dixon (Chapter One, "General Principles", In THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 4th edition, L.S. Goodman and A. Gilman, Eds. (1970)) (Hecht Declaration Exhibit 2) that "[n]o drug is free of toxic effects." They further state, however, that "adverse effects do not arise solely because of the inherent toxicity of drugs and the limitations of the methods for early detection of this toxicity. *Many of the adverse effects could be avoided if drugs were used more carefully and more wisely.*" *Id.* at 26 (emphasis added). Further, "[t]he development and evaluation of new drugs in the United States is rigidly controlled by federal regulation administered by the Food and Drug Administration. A new drug may not be marketed for general clinical use until it has been subjected to thorough clinical pharmacological studies and until 'substantial evidence' of its efficacy and safety have been obtained from adequate, well-controlled clinical trials conducted by qualified investigators." *Id.* at 29.

Since both positive and negative results must be included in data packages submitted to regulatory agencies, pre-clinical and clinical trials are not performed haphazardly with selective omission of negative results. In other words, slapdash animal studies are not performed for potential human therapeutic applications because all data collected is subjected to FDA scrutiny. Accordingly, every study is implemented pursuant to highly rigorous standards and carefully planned conditions. Animal tests suitable to regulatory agency submission require established animal colonies and adequate animal care facilities with appropriate veterinary oversight, the development of which is expensive and time-consuming. Accordingly, careful animal experiments do not yield large volumes of publications that appear in the literature quickly. They require systematic studies that may take years to

accomplish. In other words, a significant delay in the reporting of pre-clinical or clinical results is entirely routine in the field of drug discovery and development.

Dr. Hecht also affirms that the numerous clinical investigations conducted on *in vivo* antisense methodologies underscore the belief of pharmaceutical companies and, hence, the skilled scientists that comprise them, in the efficacy of antisense technology *in vivo* as detailed by the present application. "Big" pharmaceutical companies became interested in antisense technology after the small pioneer companies confirmed its validity. For example, pioneer companies Hybridon Inc. and Isis Pharmaceuticals, Inc. were incorporated in 1989 for the purpose of developing antisense therapeutics. Gilead Sciences, Inc. formed in 1987 for the same purpose. Genta Inc. was established as a spin-off of Gen-Probe in 1988 with a business objective of developing antisense therapies initiated in Gen-Probe's diagnostic antisense studies. In the mid- and late 1990s, newcomers MethylGene Inc., Inex Pharmaceuticals Corp., and NeoPharma, to name only a few, joined the early-stage companies in exploiting the therapeutic aspects of antisense technology.

In contrast, as explained by Dr. Hecht, while contributing early-published papers regarding *in vitro* related research topics, individual academic researchers, who contribute much of the scientific literature, did not exploit and publish *in vivo* antisense technology. The reasons for this are varied. The exorbitant costs of animal studies, resulting from the necessity of numerous controls as well as the stringent regulations imposed by academic institutions and regulatory agencies, preclude most academic researchers from pursuing such studies absent industrial sponsorship. Additionally, the experiments conducted by most academicians are limited in scope by narrow, well-delineated areas of research interest. Accordingly, academic researchers do not perform isolated experiments that have no bearing

on that research interest. Rather, academics are selective in choosing the focus of their experiments, limiting their experimental objectives to the particular area of research that fits into the grand scheme of the research to which their careers are dedicated, for which they have received institutional approval to study, and for which they have been granted funding.

Dr. Hecht summarizes that antisense technology was developed by small, early stage companies having limited resources. In view of the need of such companies to conserve their limited resources and the knowledge of such companies that a single poorly planned trial yielding a negative outcome could devastate an entire business venture, the pioneer companies in the antisense field had every incentive to perform animal trials carefully and systematically. They conducted animal trials in a highly methodical manner and at timepoints dictated by scientific and business judgment to advance to that phase in the process of moving their drug candidates toward IND status. Pharmaceutical companies, including Isis Pharmaceuticals, Genta Inc., and Hybridon Inc. and their present or past large pharma partners including Novartis, Lilly, Abbott, Merck, Aventis, Amgen, Roche, and Boehringer Ingelheim, have invested huge amounts of time and money to verify the efficacy of antisense drugs in an effort to propel them through clinical phases and into the market. Given the enormous costs associated with drug development and marketing, pharmaceutical companies would not have invested so heavily in the development of antisense technologies if they believed antisense molecules would not work *in vivo*.

Indeed, clinical trials of antisense therapies have definitively established that antisense technology does work *in vivo* in accordance with the principles and guidance set forth in the present application. For example, positive results have been obtained with the antisense drug Fomivirsen (Isis Pharmaceuticals, assignee of the present application), as

substantiated by the approval thereof for the treatment of cytomegaloviral-induced retinitis by the FDA in 1998. More importantly, the Investigational New Drug Application (IND) for Fomivirsen was filed with the FDA in 1993, three years prior to publication of the Rojanasakul reference. Pre-clinical data was included as part of the IND. Thus, prior to the publication of the opinions of skeptics now relied upon by the Examiner, those skilled in the art already had obtained and submitted *in vivo* data to the FDA, data supporting results contravening that opined by the skeptics. Thus, prior to publication of the negative opinions of skeptics, those skilled in the art had accomplished that which the skeptics opined would not work. In other words, those of skill in the art already were gathering *in vivo* data in support of their IND well before the publication of the opinions of antisense skeptics relied on by the Examiner.

That incorrect criticism by naysayers of antisense technology may have been posited since the effective filing date of the present application is of no relevance to the enablement of the solicited claims. Criticism of advances in science and technology will exist. That critics of Christopher Columbus's founded statement that the world was round quipped that the world was indeed flat made Christopher Columbus no less correct. Likewise, the opinions of skeptics such as Gura and Rojanasakul make Applicant no less correct in his founded and proven statement in 1981 made via the present application that antisense technology using both single- and double-stranded oligonucleotides works *in vivo*. The invention as set forth in the application and as presently claimed has been proven to work time and again in the years following the effective filing date of the present application. No further disclosure than that made by Applicant in 1981 was necessary to practice the invention as presently claimed. Applicant was absolutely correct in 1981 and has been

proven correct repeatedly thereafter. No clearer case of satisfaction of the enablement requirement of 35 U.S.C. § 112 can be shown. Applicant has satisfied his burden and requests reconsideration and withdrawal of the rejection.

V. The Obviousness - Type Double Patenting Rejection of Claim 71 is Improper

Claim 71 has been rejected for alleged obviousness-type double patenting. Applicant disagrees. This rejection will be more formally addressed by Applicant upon the indication of allowable subject matter.

REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 C.F.R. § 1.129

CONCLUSION

Applicant has presented claims that will give him the patent protection to which he is entitled. The present claims meet all requirements for patentability, and Applicant is entitled to issuance thereof. If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-568-3100.

Respectfully submitted,

Date: March 7, 2003

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Attachments
- Exhibit A
- Declaration of Dr. Sidney M. Hecht Pursuant to 37 C.F.R. § 1.132 and accompanying Exhibits 1, 2, 3, 4, 5, 6, and 7
- Notice of Appeal